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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,407	08/01/2003	Douglas W. Losordo	58098 (71417)	6007

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,407	LOSORDO ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,14-16,20,22,23,28,29,35,43-65 and 69-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,11-13,17-19,21,30-34,36,37,40-42 and 75-80* is/are rejected.

7)☒ Claim(s) *24-27, 38-39, 66-68, and 81-83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/2009 has been entered.

2. Claims 1-83 are currently pending, with claims 4-7, 10, 14-16, 20, 22-23, 28-29, 35, 43-65, and 69-74 withdrawn as non-elected subject matter. Claims 1-3, 8-9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, and 75-83 the subject of this office action.

Claim Objections

1. Objection to claim 30, as set forth on page 2 of the office action mailed on 10/1/2008, is *withdrawn* in view of Applicants' amendments to the claim to recite "blood vessels, wherein".

2. Objection to claim 80, as set forth on page 2 of the office action mailed on 10/1/2008, is *withdrawn* in view of Applicants' amendments to the claim to recite "The method of claim 30, wherein".

3. Objection to claim 82, as set forth on page 2 of the office action mailed on 10/1/2008, is *withdrawn* in view of Applicants' amendments to the claim to recite "wherein the endothelial cells".

4. Due to Applicants' amendments to claim 1 to recite methods of decreasing ezrin activity, the Examiner suggests amending the claim to recite administration of an "ezrin inhibitor" or something similar, rather than an "ezrin modulating" agent.

5. Claims 24-27, 38-39, 66-68, and 81-83 are objected to for depending from rejected base claims.

Claim Rejections - 35 USC § 112, first paragraph – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 1-3, 8-9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, and 75-83 under 35 USC § 112, first paragraph, regarding lack of enablement for methods of modulating endothelial cell proliferation comprising administration of an ezrin-modulating agent, as set forth on pages 4-6 of the office action mailed on 10/1/2008, is *withdrawn*.

In the response received on 3/2/2009, the Applicants note that independent claims 1 and 17 have been amended to recite methods comprising *decreasing* ezrin activity, "before, during, or after the mammal is exposed to conditions conducive to damaging blood vessels." The Applicants argue that the data presented within the instant specification shows that it is possible to modulate/decrease ezrin activity by administration of ROCK-2 inhibitors, and that this is correlated in vivo with inhibition of ezrin activity leading to increased endothelial cell proliferation, angiogenesis, and formation of blood vessels. Thus, the claimed pharmacological activity is reasonable based on the probative evidence provided by the specification. The Applicants also cite several references (Krasinski *et al*, Beutler *et al*, Lin *et al*) showing that inhibition/blocking of TNF improves re-endothelialization after balloon angioplasty, that TNF inhibits endothelial cell proliferation and mediates cell cycle arrest of endothelial cells, and that the cyclin A promoter is believed to harbor regulatory elements that facilitate cell cycle control and transcription of this gene. Combined with the disclosure in the specification that ezrin inhibits TNF inhibition of transcription via the cyclin A promoter which prevents TNF from mediating cell cycle arrest, inhibition of ezrin would counter this inhibition by TNF resulting from balloon angioplasty and other conditions conducive to damaging blood vessels.

Furthermore, the Applicants argue that the references cited in previous office actions do not sufficiently support a finding of non-enablement. For example, the Applicants assert that the data of Uchida *et al* relates to endothelial cells grown in culture and thus are not relative to the claimed invention, and that the methods of data analysis employed by Uchida call into question the validity of the conclusions. The Applicants also argue that Xue *et al* relates to cancer rather than angiogenesis that is induced before, during, or after blood vessel damage. Similarly, the Applicants assert that the model employed by Hata *et al* is not relevant to the claimed method because in this model, efforts are made to limit damage to the cornea in order to prevent an inflammatory response. Finally, the Applicants cite

Wolfrum et al, which shows that inhibition of Rho kinase, which in turn results in the inhibition of ezrin, provides cardiovascular protection in two ischemia reperfusion injury models, one of which was myocardial ischemia which causes damage to blood vessels. Therefore, the Applicants assert that the specification clearly demonstrates that upon vascular injury, which includes inflammation and TNF release, decreasing ezrin activity increases cell proliferation which is clearly distinct from the cited art in which the activity of ezrin inhibitors were tested in the absence of inflammation.

These arguments have been fully considered and are persuasive.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8-9, 11-13, 17-19, 21, 30-34, 36-37, 40-42, and 75-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Shibata *et al* ("Shibata" - *Circulation*, 2001 (Jan 16), Vol. 103, p. 284-289 - originally cited in the office action mailed on 8/1/06).

The claims of the present invention are drawn to methods of modulating endothelial cell proliferation in a mammal, or inducing formation of new blood vessels in a mammal, or reducing the severity of blood vessel damage in a mammal, wherein said method comprises administration of an ezrin modulating agent, and wherein said administration is before, during, or after the mammal is exposed to conditions conducive to damaging blood vessels. The claims are further drawn to the claimed methods wherein ezrin activity is decreased by an amount sufficient to enhance endothelial cell (EC) proliferation, and wherein the ezrin modulating agent reduces or blocks the activity of Rho kinase (ROCK-2) in the ECs and/or decreases ezrin DNA binding activity, and specifically, wherein the ezrin modulating agent is Y27632. The claims also recite blood vessel damage that is associated with invasive manipulation, such as balloon angioplasty, and administration of an ezrin modulating agent at various time points before and after blood vessel damage.

Shibata anticipates the indicated claims because it teaches administration of an ezrin modulating agent to rats before and after a vascular injury. Specifically, Shibata teaches administration of Y27632, which the present specification identifies as an ezrin-modulating agent, to rats which have suffered a balloon injury. Although Shibata does not explicitly teach that Y27632 is an ezrin modulating agent, it would inherently possess this characteristic, as evidenced by the instant specification (p. 26, lines 1-3) and Kishore *et al* (*J. Clin. Invest.*, 2005, Vol. 115(7), p. 1785-1796 - previously cited in the office action mailed on 8/1/06). Furthermore, although Shibata does not specifically teach methods of modulating EC proliferation, inducing formation of new blood vessels, or reducing the severity of blood vessel damage in a mammal, it is noted that the patient population in Shibata is the same as currently claimed (i.e. a mammal having a vascular balloon injury), and the method steps of administering an ezrin modulating agent (Y27632) to a mammal is the same as what is currently claimed. Therefore, in the absence of evidence to the contrary, this administration of Y27632 to balloon-injured rats would inherently lead to increased EC proliferation, formation of new blood vessels, and reduction of the severity of blood vessel damage. Furthermore, this administration of the ezrin-modulating agent Y27632 to rats suffering from a vascular balloon injury would also be expected to decrease ezrin activity by an amount sufficient to enhance EC proliferation, and the Y27632 would also be expected to reduce or block ROCK-2 activity in ECs and decrease ezrin DNA binding, as evidenced by Kishore *et al*, which shows that Y27632 abolished ROCK-2 phosphorylation and inhibited TNF-α CHR-binding activity of ezrin (p. 1788, 2nd column). For these reasons, the limitations of claims 1-3, 8-9, 17-19, 30-31, 33-34, 36-37, and 75-76 are inherently met by the disclosure of Shibata. Additionally, although Shibata does not disclose determining ezrin activity using a standard cyclin A promoter binding assay, a ezrin mRNA stability assay, or a tyrosine phosphorylation assay, as recited in claims 11-13, it would be expected, in absence of evidence to the contrary and for the reasons discussed above, that the administered Y27632 of Shibata would inherently decrease ezrin activity as assessed by these methods in a manner that meets the limitations of these claims.

Regarding claims 21, 32, and 40-42, it is noted that Shibata teaches administration of Y27632 by intraperitoneal injection 1 day before balloon injury and then for 4, 7, or 14 consecutive days after balloon injury (p. 285, 1st column, 1st full paragraph). In absence of evidence to the contrary, the administered Y27632 would be expected to contact ECs, inherently leading to a decrease in ezrin activity in these cells, and in the absence of a preferred definition of "near", the Y27632 could be considered as being administered "near" the site of blood vessel damage.

Regarding claims 77-80, although Shibata does not explicitly disclose that the balloon-injury model resulted in EC exposure to TNF-α, the specification teaches that TNF-α is expressed in arteries after balloon injury (p. 3, lines 1-4). Thus, the method of Shibata would be expected to have resulted in inflammation and subsequent exposure of ECs to TNF-α.

Finally, it is noted that Kishore is not being used as a grounds of rejection, but to provide evidence regarding the inherent properties of Y27632.

Conclusion

Claims 1-3, 8-9, 11-13, 17-19, 21, 30-34, 36-37, 40-42, and 75-80 are rejected.

Claims 24-27, 38-39, 66-68, and 81-83 are objected to for depending from rejected base claims, but would otherwise be allowable if written in independent form to include all of the limitations of the base claim(s).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647